REMARKS

Claims 1-12, 20 and 24-29 are in the case. Claims 28 and 29 are new. Claims 13-19 and 21-23 were previously withdrawn from consideration. The Examiner is thanked for her phone conversation with the undersigned on or about October 5, 2007, in which she indicated that the stated rejection under Section 102(e) at the top of page 12 of the Office Action was reiterated in the Office Action erroneously, and that it should be withdrawn. Confirmation of withdrawal of that rejection is requested in the Examiner's next correspondence with the Applicants.

Paragraph 0009 of the Specification has been amended to correct the number of amino acids in the sequence disclosed, since the actual listed number extends from amino acid 20 to amino acid 83. There is no new matter added by this amendment, since the same sequence is disclosed in the reference cited in paragraph 0009 and incorporated by reference at paragraph 0124.

Claim 1 has been amended. Support for the amendment to Claim 1, as well as for new Claims 28-29, can be found in the Specification at least at paragraphs 0038, 0042, 0044, 0050 and 0051. No new matter is added by these amendments and they are otherwise proper.

Claim 3 has been amended to correct a typographical error in the claim set presented with the claim amendments filed by Applicants on July 5, 2007. The original Claim 3 correctly referred to the β chain, but the July 5, 2007 claim set included a typographical error so that the claim inadvertently referenced the α chain in Claim 3. The present amendment thus merely places Claim 3 back into its original form. This amendment obviates the Examiner's objection to Claim 3 under Rule 75 stated on page 12 of the Office Action.

Claims 4 and 27 have been amended to specify that the oligomer forming coil-coiled protein is COMP. Support for these amendments can be found at least at paragraphs 0022, 0028 and 0041 of the original Specification. No new matter is presented by these amendments and they are otherwise proper.

Claims 6, 8 and 10 have been amended to correct the typographical errors noted by the Examiner, without adding new matter.

Reconsideration of this application and the amended claims is requested in view of the following additional remarks.

Examiner Objection – Trademark Usage

At item number 3, page 2 of the Office Action, the Examiner has objected to the presence of the word "Mini-prep" in the patent application at paragraph 0095, alleging that this is a trademark. However, in the context of paragraph 0095, "mini-prep" is a adjective which is not actually a trademark, but rather refers to plasmid miniprep kits or methods marketed under the trademark, as indicated in paragraph 0095, of QIAPREP, by Qiagen N.V. For more information, the Examiner is invited to see the Qiagen website at http://www.qiagen.com. In view of these facts and those readily available from the aforesaid website, the Examiner's objection to the use of "Mini-prep" in paragraph 0095 appears to be misplaced, and should be reconsidered and withdrawn.

Examiner Objection – New Matter

The Examiner has objected to the amendments presented by Applicants on July 5, 2007, on the basis of the allegation that the amendments introduce new matter in violation of 35 U.S.C. 132(a). In view of the foregoing amendments, this objection, with respect to the subject matter identified in the Office Action in section 4(a) – (c), is made moot and should be reconsidered and withdrawn.

Section 112 Written Description (New Matter) Rejection of Claims 5 and 25

Claims 5 and 25 stand rejected as allegedly violating the new matter limitations and written description requirement under 35 U.S.C. § 112, first paragraph. In view of the foregoing amendments, the rejection is now moot. This rejection should therefore be reconsidered and withdrawn.

Section 112 (Written Description) Rejection of Claims 4 and 20

Claims 4 and 20 are rejected as allegedly failing the written description requirement under 35 U.S.C. § 112, first paragraph, because the claims are directed to subject matter allegedly not sufficiently described in the disclosure of the original Specification. The precise reasoning of the Examiner in this rejection is difficult to follow from the Office Action. However, as best as can be understood, this rejection is respectfully traversed.

The Examiner, at the head of page 5 of the Office Action, states that

> [s]ince the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is **highly variant**, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.
> (Emphasis added.)

The Examiner's assertion that COMP genus is "highly variant" is made without any support whatsoever.

Moreover, one may simply review protein databases to compare the COMP sequences of other species and note that COMP is not highly variant. For example, the mouse, rat, human, bovine, horse and chimp like monkey COMP oligomerization domains and full protein sequences (and associated accession IDs), along with an analysis of homologies, are set out in the attached **Appendix**, prepared by co-inventor Dr. Schwabe. (If Examiner would prefer this data to be presented in the form of an affidavit from Dr. Schwabe, please notify the undersigned.) The sequences cited are all the known COMP sequences from mammalian species from the Swiss-Prot UniProt databases available on the website at http://www.expasy.org. They can be called up at the following URL: http://www.expasy.org/cgi-bin/get-sprot-entry?IDENTIFIER, where the IDENTIFIER is one from the accompanying **Appendix**. As can be seen from the **Appendix**, the rat sequence in the region 20-83 matches aligned mouse, bovine and horse sequences to 98% (Mouse), 89% (Bovine), 88% (Horse) and the human sequence matches the Chimp sequence 97%. While the Chimp sequence was apparently not known prior to the Applicants' priority date, all other sequences were known, according to the content of the Swiss-Prot UniProt databases on the internet. Based on the high homology clearly evident, the practitioner of ordinary skill in the art would assume that these proteins have the same structure function. There are further no suggestions to the contrary in the literature, so far as is known.

The human sequence has a homology with the rat sequence of 78%. Within the known COMP sequences for mammalian sequences, Applicants' have therefore given two examples that span the spectrum of differences in terms of homology by giving human and rat COMP as examples. Applicants' example for human COMP demonstrates that the structure function is conserved between human and rat COMP. It is therefore reasonable to assume, for the practitioner of ordinary skill in the art at the time of this invention, that sequences from other mammalian species that have a higher homology with either human or rat comp will also conserve the structure function of this core region.

It should also be pointed out that the COMP specified in Claims 4 and 20 must be one from which the oligomerizing domain of Claim 1 is derived. In other words, even in the absence of other information these claims are limited to COMP proteins that are oligomers-forming coiled-coil proteins with an oligomerizing domain, thus clarifying the structure function requirement of these proteins in this regard.

Finally, the case law cited at page 4 of the Office Action in respect of the issue of support of genus is misplaced. For example, the *Amgen v. Chugai* decision relates to a case where the applicant attempted to claim any cDNA sequence in any species that codes for a particular protein or an analogue thereof without reciting a single example for a specific cDNA sequence meeting that requirement. There is a very high potential degeneracy in such sequences, including codon degeneracy, codon species dependency, variations in exon and intron sequence composition. This scenario is far removed from the present situation, dealing with protein sequences only and with a conserved genus such as the oligomerisation domain of COMP.

For at least these reasons, Claims 4 and 20 are fully supported and sufficiently described, to their full scope, by the written description original filed in this case, and this rejection should be reconsidered and withdrawn.

Section 103(a) Rejection of Claims 1-12, 20 and 26

Claims 1-12, 20 and 26 stand rejected as allegedly obvious over WO 99/21572 A1 in view of five different references, namely (a) WO 98/18943 A1; (b) Terskikh et al. (PNAS USA 1997, 1663-1668, IDS Reference) (hereinafter "Terskikh") (c) Mueller et al. (Meth.Enzymol. 2000, 326, pgs. 261-268, IDS Reference) (hereinafter "Muller et al."); (d) Efimov et al., FEBS Letters 1994, 341: 54-48, of record (hereinafter "Efimov et al. *I*"); and (e) Efimov et al., Proteins 1996, 24: 259-262, of record (hereinafter "Efimov et al. *II*"). This rejection is respectfully traversed.

The Examiner in the Office action (Section 12 page 6 3d paragraph on page) claims that WO 98/18943 A1 teaches fusing COMP to an scFV fragment. We respectfully submit that this is not correct, and believe that the Examiner now agrees with Applicants in this regard, in view of the discussions the undersigned and one of the inventors, Dr. Schwabe, had in the telephonic interview conducted on March 4, 2008. The same is then true of Terskikh et al. since Terskikh et

al. is essentially the scientific publication on substantially the same subject matter as WO 98/18943 A1.

In view of the discussions had with the Examiner during the aforesaid interview, it appears that the remaining inquiry with respect to the issue of obviousness of the claimed invention is whether one of ordinary skill in the art at the time of this invention would have found it obvious to combine the teachings of WO 99/21572 A1 and Mueller *et al.* to arrive at the present invention, without the benefit of the present disclosure. Such a combination would not have been obvious to such person having ordinary skill in the art, for at least the reasons explained herein below.

Initially, Applicants note that the cited references in no way could have enabled a person having ordinary skill in the art to practice the present invention. The physical and chemical differences between MHC complex and the higher order ($n > 2$) oligomer-forming coiled coil proteins of the prior art allegedly supporting the present rejection present unique challenges to the multimerization of MHC complex monomers, and there is absolutely nothing in the cited prior art or the assertions made by the Examiner which would suggest how one of ordinary skill in the art might carry out the multimerization necessary to achieve the presently claimed invention, without the benefit of Applicants' disclosure.

Furthermore, in the Office Action, the Examiner states that

> One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 99/21572 Al teaches an MHC oligomeric complex containing coiled-coil domains and the advantages of using them to increase avidity of MHC complexes, [...]. Muller et al teach the versatility and stability of coiled-coil domains for oligomerizing proteins, the advantage of increased avidity that their use provides, and their use in various diagnostic and therapeutic applications.

Reference to Muller *et al.* is made earlier in the Office Action at the head of page 7, reading:

> Muller et al teach that chimeric multimers made by genetic fusions to heterologous oligomerization domains can be constructed with coiled coils that act as versatile fusion partners, having small domains with predictable quaternary structure and adjustable stability (especially first paragraph). Muller *et* al teach that the best-characterized pentamer occurs in COMP (especially page 264, last sentence at the end of the first full paragraph). Muller *et* al. teach using coiled coils to generate chimeric proteins with higher avidity (especially paragraph spanning pages 267-269). Muller et al teach that the coiled coil can be genetically fused to the protein of interest via a flexible linker (especially first sentence on page 269). Muller *et* al teach adding fluorescent labels to the multimers, and use

of the multimers for numerous biochemical, genetic, diagnostic and therapeutic applications (especially page 281 at the last two paragraphs).

We respectfully disagree with the Examiner's assertion that Muller *et al.* adds to the expectation that the MHC oligomers of claim 1 would be rendered obvious when Mueller is combined with WO99/21572 for the following reasons.

The '572 reference on page 12 thereof last paragraph starting on page states:

"The term "joining molecule" as used herein in reference to a polyspecific MHC complex of the invention refers to a protein or polypeptide that is capable of specifically binding and forming a specific binding pair, either covalently (e.g. by disulfide binding or non-covalently by hydrogen bonding with another protein or polypeptide. Typically, a molecule which is specifically bound by the joining molecule is sometimes referred to herein as a second joining molecule, which second joining molecule is the same as, or different from, the (first) joining molecule. Examples for joining molecule include immunoglobulin constant chains (H or L) or suitable fragments thereof, as well as coiled-coil and helix turn helix motifs such as those described more fully below."

'572 on page 30 discloses multi chain polyspecific MHC class I and class II molecules of the formula

A-B1-C1
  ||
D-B2-C2

wherein A and D are single chain MHC class I or class II molecules that may be the same or different, B1 and B2 may be the same or different joining molecules, C1 and C2 may be the same or different effector molecules.

From the above two sections, namely the reference to "specific binding pair" and the B1 = B2 bridge drawing in the figure it is intrinsically clear that '572 refers to dimeric joining molecules only.

On page 33 at the bottom of the page it is mentioned that the joining molecules can include a protein-protein binding motif such as, e.g. a helix turn helix leucine zipper motif. The only example of such a leucine zipper embodiment given in the reference recites the molecules fos and jun which are described much more specifically in the example 14 on page 96, where explicit sequences for fos and jun fusion partners are given. Following the example therefore may yield dimers of an MHC molecule which whereby the dimer may or may not have the same specificity in each of its MHC molecules.

The fos-jun leucine zipper combination however can only lead to a low-valent dimeric MHC peptide complex which does not as such provide a significant advantage of the Ig-fused dimeric MHC molecules described in the prior art reference WO93/10220.

Para 0038 of the description of the present invention explains that:

> "[..] it is believed that this increase in affinity is achieved when three or more MHC molecules are arranged substantially in the same plane with all binding faces oriented in the same direction."

The conceptual use of fos and jus leucine zipper molecules to generate homo or hetero dimeric MHC molecules of '572 seems to be a follow-on step from the previous use of such dimeric leucine zippers such as in the previously cited reference like US2005/0003431 (431) where these heterodimeric leucine zipper molecules were used to stabilize hetero-dimeric MHC monomers by fusing MHC alpha and beta chains to one and the other of fos and jun respectively. The applicants of '572 presumably knew the fact that dimeric leucine zippers had been used to stabilize hetero-dimeric MHC monomers thought that these leucine zipper molecules could also potentially replace dimeric Ig domains as a fusion partners to construct a heterodimers of MHC molecule complexes.

However, the skilled practitioner, at the time would have been keenly aware of the potential difficulties that would be a consequence of combining a more complex higher order multimeric structure with the structure of an MHC molecule to generate higher order MHC multimers, especially when such higher a multimeric structures had never been used in the context of MHC. The higher order (n>=3) MHC- coiled coil oligomers of the present invention are a quantum leap in this regard combining a multimerization domain of capable of generating uniformly high valence with the complex structure of a fully assembled MHC peptide complex.

As to the reference of Muller *et al.*, it states that "[t]he versatility of coiled coils for oligomerisation derives from their diversity of oligomeric structures." (Muller *et al.*, page 261, last paragraph. Emphasis added.) In effect this diversity means that the coiled coils are very different from one another with different properties. This diversity in property would however make the outcome of an attempt to fuse any particular type of coiled coil to any other particular category of protein inherently uncertain.

The fact that the coiled coil domains are relatively small may be an advantage in some of the oligomers that have been constructed, but the property of size of the oligomerisation domain

in itself cannot be taken to mean as such that success of using a coiled coil protein in a fusion protein can be predicted.

Specifically the Muller *et al.* reference first discusses coiled coil proteins and their properties as such on pages 261-264. It states that coiled coils can have dimer, trimer, tetramer and pentamer structures. It also states that "[t]he best characterized pentamer occurs in cartilage oligomeric matrix protein COMP." (Muller *et al.*, page 264, end of second full paragraph; cf. the comment of the Examiner.) In other words, this last statement reiterates that coiled coil proteins can be pentamers and that COMP is the best characterized pentameric coiled coil protein. (Interestingly, Muller *et al.* also refers to COMP generically without linking or limiting it to any particular species.) However, what this statement as such does ***not*** do is to make any comment on the extent to which COMP can be used to produce pentameric ***fusion*** proteins. In this manner, this comment does not add anything to the references of Efimov, which simply explains and characterizes the properties of COMP itself.

The Examiner states that, on page 269 of Muller *et al.*, the reference teaches that the coiled coil can be genetically fused to the protein of interest via a flexible linker. This statement simply explains that constructing a fusion protein would involve making a genetic fusion of the proteins of interest in an expression construct and that a linker sequence could be interposed between the coiled coil section and the relevant fusion partner. It is of course generically true that any oligomerisation domain from any protein could be fused to any other sequence from any other protein and expression could be attempted. But no inference can be made from this statement as to the likely chance of success for the protein fusion protein being expressed successfully with the desired structure and function.

Explicit examples for coiled coil ***fusions*** only start on the bottom of page 267 of Muller. There it is stated in the second sentence that:

> The most straightforward application [of coiled coil fusions] is replacement of natural oligomerisation domains. Examples are given for the dimerisation domain of phage lambda repressor, the constant region of antibodies and the trimerisation domain of CD40 ligand.

In fact, with the exception of the reference of Terskikh with the short, structureless peptides, for structures that are oligomers which are trimers (CD40 / CD40L), or higher valency fusion (tetramers), ***only naturally oligomeric molecules are discussed*** as fusion partners for

oligomerization through coiled coil proteins. This must be contrasted with MHC complexes, which are naturally intrinsically monomeric complexes anchored in the cell surface.

Table I on page 272 of Muller *et al.* and following pages, lists the following homotrimers of proteins:

Homotrimer

IL-2R: This is a naturally trimeric molecule

HIV-1 gp41 and Ebola membrane fusion protein GP2 (see also Fig 3 on page 280) These proteins are trimeric coiled coil proteins.

CD40L – this is a soluble trimer (see comment right hand side column)

Heterotrimer

IL2-R: This is a trimer as already mentioned above.

Homotetramers

scFv antibody fragment. This case is also described on page 276. The reference specifically states, "Antibodies are at least bivalent as in the case of the IgG molecule and in the early immune response the decameric IgM molecules provide the primary defense."

Since IgG antibodies arise as a consequence of the affinity maturation and isotype switching from IgM antibodies the Ig binding domain design is intrinsically suitable for multimerisation in several degrees (IgG: n=2, IgM: n=10, IgA: n=4). Further scFv fragments are still much more likely to refold on their own than MHC molecules since they are intrinsically smaller and substantially less complex in structure than MHC molecules.

P53 1-343 to substitute the tetramerisation domain of p53.

Homopentamer

Reference is made to Terskikh et al. in respect of using COMP. However, this is the only actual reference cited for any COMP fusion.

In contrast to the intrinsically multimeric proteins that have been fused to coiled coil proteins in the examples given by Muller et al., MHC molecules are *intrinsically monomeric complexes* on the cell surface and they *do not comprise any natural multimerisation domain.*

The specific example on page 278, last paragraph starting on page, second sentence of Muller *et al.* states in the context of a scFv GCN fusion:

> For scFv fragments that tended to aggregate, bringing together two or more molecules resulted in poor to very poor yields, bringing together two or more molecules resulted in poor to very poor yields.

This hints at the problems a skilled practitioner would have expected to experience with MHC molecules in hypothetical coiled coil fusions. MHC molecules due to their size have many hydrophobic surfaces. COMP and other coiled coil proteins have extremely hydrophobic surfaces, which for these proteins in isolation confer their good stability when they are properly folded. In any heterologous fusion of coiled-coil to MHC complex, a multitude of very hydrophobic domains are juxtaposed during and/or following expression and the likelihood for aggregation is exacerbated very significantly, especially for n>2, even compared to the still rather simple example of the reference. The skilled practitioner would have had no guidance from the cited references and no reason to believe that any improvement by varying expression systems would have been sufficient in order to generate complexes of the presently claimed invention, with a useful function.

With respect this particular property of MHC molecules, it would not have been obvious to consider combining MHC molecules with higher order coiled coil domains (n>2). In this regard, Paragraph 6 of the opinion of Dr. Gerald Nepom filed earlier in this case is still entirely pertinent and accurate:

> 6. Beyond the reasons stated above, there were a large number of biochemical and structural reasons why a person of ordinary skill in the art at the filing date of this application would not have found the claimed invention in Claim 1, and the claims depending therefrom, obvious. These include issues of protein solubility, stereochemistry, steric inhibition with function and folding, misfolding of the macromolecular ligand, and orientation of the assembled complex. There simply was no way, *a priori*, to predict that these significant issues would actually be able to accommodate the MHC peptide structure as ligand attached to a portion of the coiled-coil protein. Nor would there have been any motivation, from the cited literature or from the body of common knowledge, for a person of ordinary skill at the relevant time to attempt such a combination with any ***reasonable*** expectation of success.
>
> (Emphasis added.)

Even assuming that the fusion of MHC to a dimeric leucine zipper has been described in WO99/21572 conceptually, the concern voiced by Dr. Nepom would still have applied universally to any more complex fusion for the purpose of generating any higher order multimers and also applies in light of all new references cited by the Examiner alone and in combination.

It should be re-iterated that Dr. Nepom is more than a person of ordinary skill in the art and also more than a person of extraordinary skill in the art. He is widely recognized by his peers as one in a group of a handful of individuals who have pushed the boundaries of the uses of multimeric recombinant MHC peptide technologies by developing Class II MHC tetramers, which are now part of the NIH tetramer core facility program. The statement of Dr. Nepom in paragraph 1 of his declaration is entirely accurate in this regard.

In summary, at best Muller *et al.* has described

(i) the properties of coiled coil domains as such, and

(ii) That coiled coil domains have been used to produce some fusion molecules of other proteins. But where these proteins were trivalent or higher, such fusions were only for proteins that are in themselves multimeric and incomparable to MHC molecules, which are intrinsically monomeric.

The MHC molecule assembles under conditions that are different from the conditions under which COMP assembles. Other than the Terskikh example, there are no examples in the cited prior art for fusion proteins that have been achieved with COMP. The key difference of the MHC molecule is that its sub-units are not very stable on their own and it can be expected that they will aggregate when fused to other hydrophobic binding partners. In contrast, proteins that are naturally oligomeric may be pre-designed to have a better chance of folding their active domains, even though they may have hydrophobic oligomerisation domains.

The historical state of the art for making MHC oligomers and the motivation for doing so is well described in an entire volume of the Journal of Immunological Methods, 2002, vol. 268, No. 1 (entire issue). This volume mainly focuses on the MHC tetramer technology first disclosed in US 5,635,363, which was by far the dominant MHC oligomer technology at the time. The article of Hugues *et al.*, pages 82-92, compares MHC tetramer technology with all other known multimerisation technologies for MHC molecules that had actually been put into practice. These are essentially limited to variations of fusions to the Ig scaffold and in one case based on a peptide cross linking reagent. None of these approaches were based on combinations with coiled

coil proteins. To Applicants' knowledge, the example of WO99/21572 creating a fusion with a dimeric leucine zipper to generate MHC dimers has never actually been put into practice. In section 11 of this reference this article briefly concludes that "[s]tandard [MHC] tetramers are now so popular that it is difficult for other multivalent reagents to compete." Since then, the MHC pentamer technology that was commercialised by the assignee of the present application and employer of Applicants in 2003 and that is based on the present disclosure has become the only other MHC multimer technology which has been able to successfully compete with and improve on MHC tetramers. Use of the Applicants' assignee's Pro5® MHC pentamers is now published at twice rate in scientific publications as the use of MHC tetramers from the applicant's strongest competitor in this field, Beckman Coulter, Inc. The publication rate for Pro5® MHC pentamers is also a multiple of that of any other MHC oligomer technology. No functional MHC oligomers that rely on use of a coiled-coil domain for oligomerisation other than Pro5® MHC pentamers have ever been published, so far as is known.

In summary, reading the Muller and '572 references in combination would not have led the skilled practitioner to consider how to otherwise arrive at higher order multimers through coiled coil structures. Muller by reference through Terskikh and Terskikh and WO 98/18943 A1 (the latter two of which are virtually identical) read in combination all would have discouraged the use of COMP in combination with a large complex fusion partner (namely, MHC). Overall, considering all the facts carefully, and in line with the clear statements made in the declaration of Dr. Nepom, the person having ordinary skill in the art would have had to cross a wide chasm between theoretical description in '572 of using fos-jun leucine zippers as hetero-dimeric MHC fusion partners and the teachings of Muller *et al.* and/or the aforementioned COMP related references for generating COMP fusions to short, structureless peptides to arrive at Applicants' invention as presently claimed. For at least these reasons, the person of ordinary skill in the art did not have, and could not have had, any teaching, suggestion or motivation, from the body of common knowledge available in the art at the time of this invention and from the combination of the cited references, to cross this wide chasm with a reasonable expectation of success. Accordingly, this rejection does not present a *prima facie* case of obviousness with respect to the claims, as amended, and should be reconsidered and withdrawn.

Section 103(a) Rejection of Claims 24, 25 and 27

Claims 24, 25 and 27 stand rejected as obvious over WO 99/21572 A1 in view of WO 98/18943 A1, Terskikh et al., Muller et al., Efimov I and Efimov II, and further in view of Disner et al., Newton et al. and admissions allegedly made in the instant Specification at paragraphs 0097 and 0098. Claim 25 is of course cancelled. This rejection with respect to Claims 24 and 27 is respectfully traversed. For all of the previously stated reasons set forth above, which are reiterated here by reference, no combination of the 572, 943, Terskikh et al., Muller et al., Efimov I and Efimov II references could have supplied, at the of this invention and to a person of ordinary skill in the art, the necessary motivation, teaching or suggestion for arriving at Applicants' claimed invention. Efimov I and Efimov II, Disner and Newton only describe COMP sequences and their properties on their own. Accordingly, this rejection does not present a *prima facie* case of obviousness with respect to the claims, as amended, and should be reconsidered and withdrawn.

Section 103(a) Rejection of Claims 25 and 26

Claims 25 and 26 stand rejected as obvious over WO 02/070725 A1 in view of WO 99/21572 A1. This rejection is respectfully traversed. The 572 reference suffers from the same lack of relevance in this context as above-described regarding the other section 103 rejections, and those arguments are reiterated here by reference. Because the 572 reference does not teach that for which it is being cited (as noted above), it cannot support a *prima facie* case of obviousness with respect to the present claims, and this rejection should be reconsidered and withdrawn. WO 02/070725 A1 adds nothing to the reference of Muller as not a single example of any protein to be multimerised with the methods described in '725 is given and also it was published only after the priority date of the present application of 21 August 2002.

Provisional Non-statutory Obviousness-type Double Patenting Rejection

Claims 1-12 and 20 stand provisionally rejected over commonly assigned patent application 10/770,140 on the basis of obviousness-type double patenting. This rejection is respectfully traversed. Applicants do not at this time concede that the claims of the respective applications are patentably indistinct. However, it should be noted that the present application

and application number 10/770,140 were both filed in the U.S. on the same day, i.e., February 2, 2004. Since the applications were co-filed, the present application should be considered the base application for co-filed patent applications in accordance with MPEP § 804(I)(B)(1). This rejection should therefore be withdrawn to allow the present application to issue without any requirement for a terminal disclaimer.

Section 102(e) Rejection No. 2

As noted earlier, it is believed that the Examiner agrees this rejection should be withdrawn, as it was overcome in the Applicants submissions made on July 5, 2007 in this application.

In view of all of the foregoing, the pending Claims 1-12, 20 and 24-29, as amended, are believed to be in a condition for allowance. Notification to this effect would be sincerely appreciated. If any matter remains unresolved, the Examiner is invited to contact the undersigned in order to expedite any possible resolution.

Respectfully submitted,

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Appendix

COMP Sequences from www.expasy.org

Q9R0G6 Mouse COMP

```
        10          20          30          40          50          60
MGPTACVLVL ALAILRATGQ GQIPLGGDLA PQMLRELQET NAALQDVREL LRHEVKEITF

        70          80          90         100         110         120
LKNTVMECDA CGMQPARTPG LSVRPVPLCA PGSCFPGVVC SETATGARCG PCPPGYTGNG

       130         140         150         160         170         180
SHCTDVNECN AHPCFPRVRC INTSPGFHCE ACPPGFSGPT HEGVGLTFAK SNKQVCTDIN

       190         200         210         220         230         240
ECETGQHNCV PNSVCVNTRG SFQCGPCQPG FVGDQTSGCQ RRGQHFCPDG SPSPCHEKAN

       250         260         270         280         290         300
CVLERDGSRS CVCAVGWAGN GLLCGRDTDL DGFPDEKLRC SERQCRKDNC VTVPNSGQED

       310         320         330         340         350         360
VDRDGIGDAC DPDADGDGVP NEQDNCPLVR NPDQRNSDSD KWGDACDNCR SKKNDDQKDT

       370         380         390         400         410         420
DLDGRGDACD DDIDGDRIRN VADNCPRVPN FDQSDSDGDG VGDACDNCPQ KDNPDQRDVD

       430         440         450         460         470         480
HDFVGDACDS DQDQDGDGHQ DSRDNCPTVP NSAQQDSDHD GKGDACDDDD DNDGVPDSRD

       490         500         510         520         530         540
NCRLVPNPGQ EDNDRDGVGD ACQGDFDADK VIDKIDVCPE NAEVTLTDFR AFQTVVLDPE

       550         560         570         580         590         600
GDAQIDPNWV VLNQGMEIVQ TMNSDPGLAV GYTAFNGVDF EGTFHVNTAT DDDYAGFIFG

       610         620         630         640         650         660
YQDSSSFYVV MWKQMEQTYW QANPFRAVAE PGIQLKAVKS STGPGEQLRN ALWHTGDTAS

       670         680         690         700         710         720
QVRLLWKDPR NVGWKDKTSY RWFLQHRPQV GYIRVRFYEG PELVADSNVV LDTAMRGGRL

       730         740         750
GVFCFSQENI IWANLRYRCN DTIPEDYESH RLQRV
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P35444 RAT COMP

```
        10          20          30          40          50          60
MSPTACVLVL ALAALRATGQ GQIPLGGDLA PQMLRELQET NAALQDVREL LRHRVKEITF

        70          80          90         100         110         120
LKNTVMECDA CGMQPARTPG LSVRPVALCA PGSCFPGVVC TETATGARCG PCPPGYTGNG
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       130        140        150        160        170        180
SHCIDVNECN AHPCFPRVRC INTSPGFHCE ACPPGFSGPT HEGVGLTFAK TNKQVCTDIN

       190        200        210        220        230        240
ECETGQHNCV PNSVCVNTRG SFQCGPCQPG FVGDQRSGCQ RRGQHFCPDG SPSPCHEKAD

       250        260        270        280        290        300
CILERDGSRS CVCAVGWAGN GLLCGRDTDL DGFPDEKLRC SERQCRKDNC VTVPNSGQED

       310        320        330        340        350        360
VDRDRIGDAC DPDADGDGVP NEQDNCPLVR NPDQRNSDKD KWGDACDNCR SQKNDDQKDT

       370        380        390        400        410        420
DRDGQGDACD DDIDGDRIRN VADNCPRVPN FDQSDSDGDG VGDACDNCPQ KDNPDQRDVD

       430        440        450        460        470        480
HDFVGDACDS DQDQDGDGHQ DSRDNCPTVP NSAQQDSDHD GKGDACDDDD DNDGVPDSRD

       490        500        510        520        530        540
NCRLVPNPGQ EDNDRDGVGD ACQGDFDADK VIDKIDVCPE NAEVTLTDFR AFQTVVLDPE

       550        560        570        580        590        600
GDAQIDPNWV VLNQGMEIVQ TMNSDPGLAV GYTAFNGVDF EGTFHVNTAT DDDYAGFIFG

       610        620        630        640        650        660
YQDSSSFYVV MWKQMEQTYW QANPFRAVAE PGIQLKAVKS STGPGEQLRN ALWHTGDTAS

       670        680        690        700        710        720
QVRLLWKDPR NVGWKDKTSY RWFLQHRPQV GYIRVRFYEG PELVADSNVV LDTAMRGGRL

       730        740        750
GVFCFSQENI IWANLRYRCN DTIPEDYERH RLRRA
```

P49747 Human COMP

```
        10         20         30         40         50         60
MVPDTACVLL LTLAALGASG QGQSPLGSDL GPQMLRELQE TNAALQDVRD WLRQQVREIT

        70         80         90        100        110        120
FLKNTVMECD ACGMQQSVRT GLPSVRPLLH CAPGFCFPGV ACIQTESGGR CGPCPAGFTG

       130        140        150        160        170        180
NGSHCTDVNE CNAHPCFPRV RCINTSPGFR CEACPPGYSG PTHQGVGLAF AKANKQVCTD

       190        200        210        220        230        240
INECETGQHN CVPNSVCINT RGSFQCGPCQ PGFVGDQASG CQRGAQRFCP DGSPSECHEH

       250        260        270        280        290        300
ADCVLERDGS RSCVCRVGWA GNGILCGRDT DLDGFPDEKL RCPEPQCRKD NCVTVPNSGQ

       310        320        330        340        350        360
EDVDRDGIGD ACDPDADGDG VPNEKDNCPL VRNPDQRNTD EDKWGDACDN CRSQKNDDQK

       370        380        390        400        410        420
```

```
DTDQDGRGDA CDDDIDGDRI RNQADNCPRV PNSDQKDSDG DGIGDACDNC PQKSNPDQAD

       430        440        450        460        470        480
VDHDFVGDAC DSDQDQDGDG HQDSRDNCPT VPNSAQEDSD HDGQGDACDD DDDNDGVPDS

       490        500        510        520        530        540
RDNCRLVPNP GQEDADRDGV GDVCQDDFDA DKVVDKIDVC PENAEVTLTD FRAFQTVVLD

       550        560        570        580        590        600
PEGDAQIDPN WVVLNQGREI VQTMNSDPGL AVGYTAFNGV DFEGTFHVNT VTDDDYAGFI

       610        620        630        640        650        660
FGYQDSSSFY VVMWKQMEQT YWQANPFRAV AEPGIQLKAV KSSTGPGEQL RNALWHTGDT

       670        680        690        700        710        720
ESQVRLLWKD PRNVGWKDKK SYRWFLQHRP QVGYIRVRFY EGPELVADSN VVLDTTMRGG

       730        740        750
RLGVFCFSQE NIIWANLRYR CNDTIPEDYE THQLRQA
```

P35445 Bovine COMP

```
        10         20         30         40         50         60
MVLAAARVLL LTLAALGASG QGQMPLGGDL GPQMLRELQE TNAALQDVRD LLRQQVKEIT

        70         80         90        100        110        120
FLKNTVMECD ACGMQPARTP KLTVRPLSQC SPGFCFPGVA CTETANGARC GPCPEGFTGN

       130        140        150        160        170        180
GSHCADVNEC TAHPCFPRVR CINTSPGFRC EACPPGFSGP THEGVGLAFA KANKQVCTDI

       190        200        210        220        230        240
NECETGQHNC VPNSVCVNTV GSFQCGPCQP GFVGDQASGC RRRPQRFCPD GTPSPCHEKA

       250        260        270        280        290        300
DCVLERDGSR SCVCAVGWAG NGLICGRDTD LDGFPDEKLR CSERQCRKDN CVTVPNSGQE

       310        320        330        340        350        360
DVDQDGIGDA CDPDADGDGV LNEKDNCPLV RNPDQRNTDG DKWGDACDNC RSQKNDDQKD

       370        380        390        400        410        420
TDKDGRGDAC DDDIDGDRIR NPVDNCPKVP NSDQKDTDGD GVGDACDNCP QKSNADQRDV

       430        440        450        460        470        480
DHDFVGDACD SDQDQDGDGH QDSKDNCPTV PNSAQQDSDH DGQGDACDDD DDNDGVPDSR

       490        500        510        520        530        540
DNCRLVPNPG QEDMDRDGVG DACQGDFDAD KVVDKIDVCP ENAEVTLTDF RAFQTVVLDP

       550        560        570        580        590        600
EGDAQIDPNW VVLNQGMEIV QTMNSDPGLA VGYTAFNGVD FEGTFHVNTA TDDDYAGFIF

       610        620        630        640        650        660
GYQDSSSFYV VMWKQMEQTY WQANPFRAVA EPGIQLKAVK SSTGPGEQLR NALWHTGDTA
```

```
       670         680         690         700         710         720
SQVRLLWKDP RNVGWKDKTS YRWFLQHRPQ VGYIRVRFYE GPELVADSNV ILDTTMRGGR

       730         740         750
LGVFCFSQEN IIWANLRYRC NDTIPEDYEA QRLLQA
```

Q9BG80 HORSE COMP

```
        10          20          30          40          50          60
MVLSAAPVLL LALAALVSSQ GQTPLGTELG PQMLRELQET NAALQDVREL LRQQVKEITF

        70          80          90         100         110         120
LKNTVMECDA CGMQPARTPR VSVRPLAQCA PGSCFPGVAC TQTASGARCG PCPAGFTGNG

       130         140         150         160         170         180
PYCADVNECN ANPCFPRVRC INTSPGFRCE ACPPGYSGPT HEGVGMAFAK ANKQVCTDID

       190         200         210         220         230         240
ECETGQHNCV PNSVCINTQG SFQCGPCQPG FVGDQASGCR PRAQRFCPDG TPSPCHEKAD

       250         260         270         280         290         300
CVLERDGSRS CVCAVGWAGN GLLCGRDTDL DGFPDEKLRC SERQCRKDNC VTVPNSGQED

       310         320         330         340         350         360
ADRDGIGDAC DTDADGDGVP NEGDNCPLVR NPDQRNTDGD KWGDACDNCR SQKNDDQKDT

       370         380         390         400         410         420
DQDGRGDACD DDIDGDRIRN AVDNCPRVPN SDQKDSDGDG IGDVCDNCPQ KSNPDQRDVD

       430         440         450         460         470         480
HDFVGDACDS DQDKDGDGHQ DSRDNCPTVP NSAQQDSDSD GQGDACDEDD DNDGVPDSRD

       490         500         510         520         530         540
NCRLVPNPGQ EDADRDGVGD VCQGDFDADK VVDKIDVCPE NAEVTLTDFR AFQTVVLDPE

       550         560         570         580         590         600
GDAQIDPNWV VLNQGMEIVQ TMNSDPGLAV GYTAFNGVDF EGTFHVNTVT DDDYAGFIFG

       610         620         630         640         650         660
YQDSSSFYVV MWKQMEQTYW QANPFRAVAE PGIQLKAVKS STGPGEQLRN ALWHTGDTAS

       670         680         690         700         710         720
QVRLLWKDPR NVGWKDKTSY RWFLQHRPQV GYIRVRFYEG PELVADSNVV LDTTMRGGRL

       730         740         750
GVFCFSQENI IWANLRYRCN DTIPEDYEIQ RLLQA
```

A5A6P0_PANTR CHIMP like monkey

```
        10          20          30          40          50          60
MVPDTACVLL LTLAALGASG QGQSPLGSDL GPQMLRELQE TNAALQDVRE LLRQQVREIT

        70          80          90         100         110         120
```

```
FLKNTVMECD ACGMQQSVRT GLPSVRPLLH CAPGFCFPGV ACIQTESGAR CGPCPAGFTG

       130        140        150        160        170        180
NGSHCTDVNE CNAHPCFPRV RCINTSPGFR CEACPPGYSG PTHEGVGLAF AKANKQVCTD

       190        200        210        220        230        240
INECETGQHN CVPNSVCINT RGSFQCGPCQ PGFVGDQESG CQRRAQRFCP DGSPSECHEH

       250        260        270        280        290        300
ADCVLERDGS RSCVCAVGWA GNGILCGRDT DLDGFPDEKL RCPERQCRKD NCVTAPNSGQ

       310        320        330        340        350        360
EDVDRDGIGD ACDPDADGDG VPNEKDNCPL VRNPDQRNTD EDKWGDACDN CRSQKNDDQK

       370        380        390        400        410        420
DTDQDGRGDA CDDDIDGDRI RNQADNCPRV PNSDQKDSDG DGIGDACDNC PQKSNPDQAD

       430        440        450        460        470        480
VDHDFVGDAC DSDQDQDGDG HQDSRDNCPT VPNSAQEDSD HDGQGDACDD DDDNDGVPDS

       490        500        510        520        530        540
RDNCRLVPNP GQEDADRDGV GDVCQDDFDA DKVVDKIDVC PENAEVTLTD FRAFQTVVLD

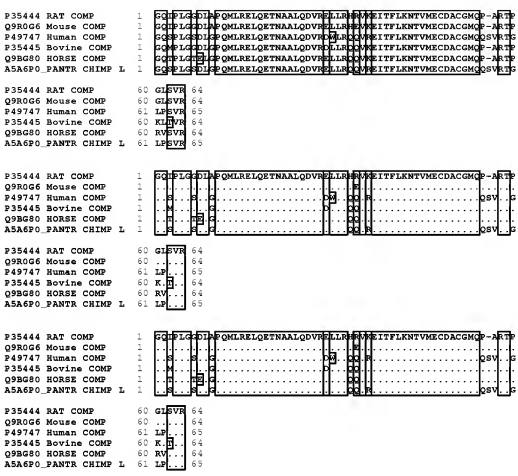
       550        560        570        580        590        600
PEGDAQIDPN WVVLNQGREI VQTMNSDPGL AVGYTAFNGV DFEGTFHVNT VTDDDYAGFI

       610        620        630        640        650        660
FGYQDSSSFY VVMWKQMEQT YWQANPFRAV AEPGIQLKAV KSSTGPGEQL RNALWHTGDT

       670        680        690        700        710        720
ESQVRLLWKD PRNVGWKDKK SYRWFLQHRP QVGYIRVRFY EGPELVADSN VVLDTTMRGG

       730        740        750
RLGVFCFSQE NIIWANLRYR CNDTIPEDYE THQLRRA
```

ClustalW sequence alignment of COMP sequences with Rat COMP amino acids 20-83



Sequence Identity Matrix for COMP domains

		Rat	Mouse	Human	Bovine	Horse	Chimp
	Seq->	P35444	Q9R0G6	P49747	P35445	Q9BG80	A5A6P0
Rat	P35444	100%	98%	78%	89%	88%	82%
Mouse	Q9R0G6	---	100%	78%	89%	88%	82%
Human	P49747	---	---	100%	83%	82%	97%
Bovine	P35445	---	---	---	100%	89%	83%
Horse	Q9BG80	---	---	---	---	100%	85%
Chimp	A5A6P0	---	---	---	---	---	100%